PEDIATRIC PHARMACOLOGY

The use of drugs in newborns, infants, and children is often based on safety, efficacy and pharmacological data generated in adults. The majority of approved drugs do not include specific dosage recommendations for children or include a disclaimer that states "safety and effectiveness in pediatric patients have not bee established." Using adult dosing recommendations in children has resulted in several therapeutic tragedies, such as the gray baby syndrome from chloramphenicol, and has illustrated that scaling adult doses to infants and children based on body weight or body surface area does not account for developmental changes that affect drug disposition (absorption, distribution, metabolism and excretion) or target tissue / organ sensitivity.

Chloramphenicol is a natural product that was isolated in 1947 from a species of *streptomyces*, a soil inhabiting microorganism. It is a bacteriostatic drug that inhibits bacterial protein synthesis. In adults, chloramphenicol is detoxified in the liver primarily through conjugation with glucuronide and a small fraction is excreted in the urine unchanged. Because of its broad spectrum of activity, it quickly gained acceptance after it was introduced into clinical practice in 1948, and it was widely used to treat a variety of infections in the 1950s, including nursery infections. In fact, because these nursery infections were with less sensitive hospital strains, adult doses scaled to the body weight and doses exceeding those recommended in adults were administered to premature and full-term infants.

In the late 1950s case reports of unexplained deaths in infants receiving chloramphenicol appeared and led to a controlled trial in premature infants born more than 24 h after spontaneous rupture of membranes. The standard of care for these infants was to treat empirically with antibiotics because of the presumed increased risk for infections. Infants were assigned to one of 4 groups depending on the time they were admitted to the nursery:

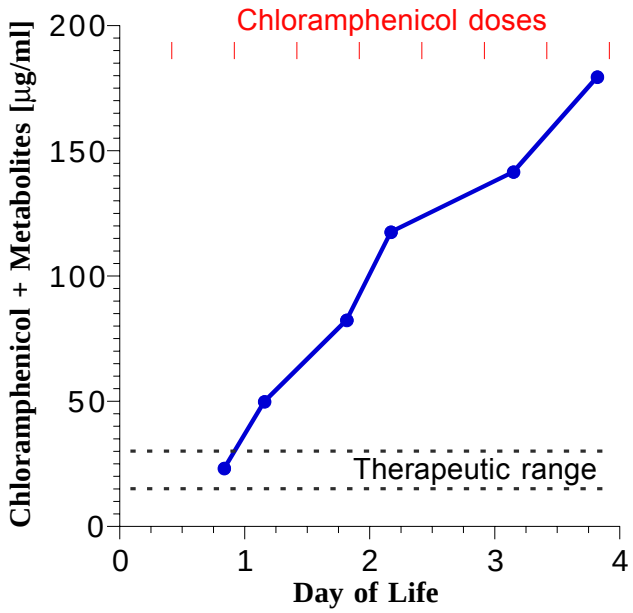
- No antibiotics
- Procaine penicillin (150,000 to 600,000 units / day) and streptomycin (50 mg / kg / d)
- Chloramphenicol (100-165 mg / kg / d IM), and
- All 3 antibiotics at the same doses

The mortality was strikingly higher in the infants receiving chloramphenicol (Table). Two thirds of the infants receiving chloramphenicol died. In the infants

	All Infants		2001-2500 gm	
	n	Deaths	n	Deaths
No antibiotics	32	6	17	1
Pen + strep	33	6	24	0
Chloramphenicol	30	19	16	8
Pen + strep + chloramphenicol	31	21	15	6

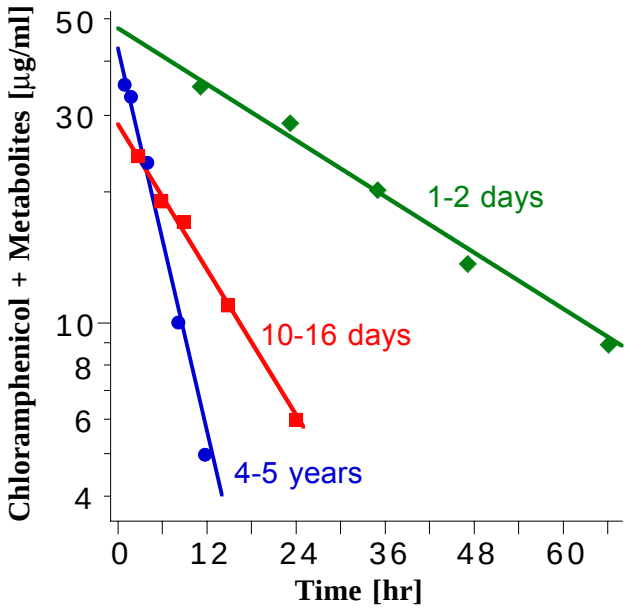
weighing more than 2000 grams at birth, 45% receiving chloramphenicol (groups 3 and 4) died compared with 2.5% in the other 2 groups. The authors to concluded that the high mortality was related to chloramphenicol.

The characteristic constellation of physical signs of chloramphenicol toxicity is known as the gray baby syndrome, and consists of vomiting, refusal to feed, respiratory distress (irregular rapid respiration), abdominal distention, periods of cyanosis, passage of loose, green stools, flaccidity, ashen color, hypothermia, vascular collapse, and death usually by the fifth day of life. 58% of the infants who received chloramphenicol and survived had similar signs, which completely resolved 24-36 hrs after stopping the drug.



After the reports of toxicity and deaths in newborns were attributed to chloramphenicol, pharmacokinetic studies of the drug were performed in newborns and children. In infants that developed toxicity, high levels of chloramphenicol and its metabolites accumulated (Figure, left), presumably due to the reduced capacity of newborns to eliminate these compounds. When studied at lower doses in a group of children over a wider age range, the elimination was highly age-dependent. The half-life was 26 hours in the newborns, 10 hours in the infants and 4 hours in the children (Figure, below).

Unfortunately, as demonstrated with chloramphenicol, the pharmacological impact of developmental changes that affect drug disposition are often discovered only after unexpected or severe toxicity in infants and children leads to detailed pharmacological studies.



Therapeutic tragedies, such as this, could be avoided by performing pediatric pharmacological studies during the drug development process (before widespread use of agents in infants and children). Despite efforts by the FDA to encourage pediatric studies and labeling (specific pediatric dose recommendations) by pharmaceutical companies on a voluntary basis, the majority

	'91	'92	'93	'94	'95	'96	Total
Drugs approved	30	25	25	22	28	53	183
Studies not required	14	11	11	7	14	13	70
Ped. labeling / studies	9	4	5	6	5	15	44
Post-approval studies requested or promised	7	10	10	10	10	17	64
Post-approval labeling	1	0	2	4	2	2	11

of marketed and newly approved drugs have no pediatric dosing information or contain only the disclaimer (Table, above). As a result of these failed efforts to gain voluntary compliance, new FDA regulations, which take effect on April 1, 1999, will empower the FDA to require pediatric studies for selected marketed drugs and new drugs that are likely to be used in a substantial number of pediatric patients or could be an improvement over current treatment of childhood diseases.

ONTOGENY AND PHARMACOLOGY

The process of growth and development of the newborn, infant and child can have a significant impact on the clinical pharmacology of a variety of drugs that are used in these pediatric populations. Significant gaps in our understanding of the relationship between ontogeny and pharmacology still remain, but an understanding of the maturation process allows for anticipation age-related changes in drug disposition and the intensity of drug effects. Maturational effects on pharmacokinetics have been more intensely studied than effects on pharmacodynamics. Changes in body mass and composition and the maturation of excretory organs have the greatest effect on drug disposition during childhood, and the most dramatic changes occur during the first days to months of life.

Drug absorption. Orally administered drugs are influenced by gastric acid secretion (e.g., acid labile drugs such as the penicillins), gastrointestinal motility, absorptive surface area, bacterial colonization of the gut and drug metabolizing enzyme levels in the intestine and liver, which are responsible for first-pass metabolism of drugs. Gastric pH is neutral at birth, but drops to 1-3 within hours of birth. Gastric acid secretion then declines on days 10-30, and does not approach adult values until approximately 3 months of age. The increased bioavailability of penicillins in the newborn has been attributed to lower levels of gastric acid secretion.

Gastric emptying is delayed and irregular in the newborn, but approaches adult values by 6-8 months. Intestinal motility is also irregular, and highly dependent on feedings patterns in newborn. The decreased GI motility in newborns can delay drug absorption and result in lower peak plasma drug concentrations, but do not alter overall bioavailability of most drugs. GI transit time may be increased in children.

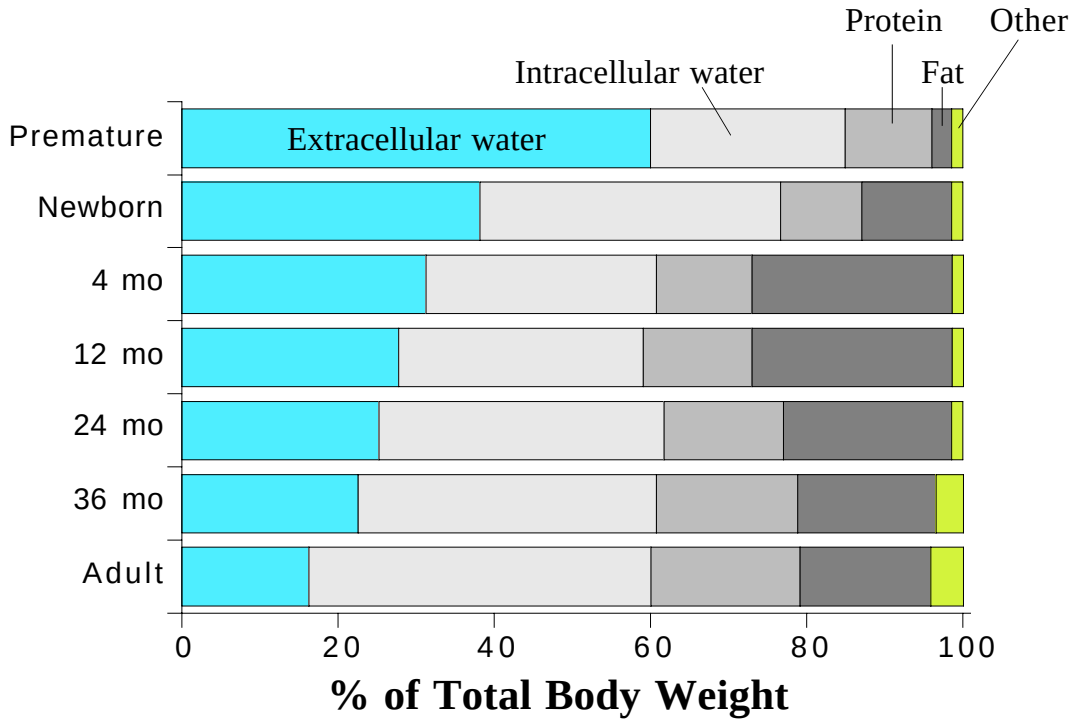
The absorptive surface area relative to body surface area is greater in infants and children than in adults. Although pancreatic enzyme excretion is low in newborns, malabsorption does not occur and no effect on drug absorption has been observed.

The newborn intestine is colonized with bacteria within days of birth, but the spectrum of bacterial flora may change over the first few years of life.

Drug distribution. The factors that affect drug distribution include physicochemical properties of the drug, cardiac output, regional blood flow, the degree of protein and tissue binding, and body composition (extracellular water and adipose tissue). Serum albumin and total protein concentrations are decreased at birth and during infancy, and approach adult levels by 1 year of age (Table). Decreased protein binding can enhance drug delivery to tissues, which is dependent on free drug concentrations. For example, the myocardium to plasma digoxin concentration ratio is 2- to 3-fold higher in neonates than in adults. The increased free fraction of drug also influences the interpretation of plasma drug concentrations relative to therapeutic ranges defined in adults, in whom a smaller fraction of the measured total drug concentrations is unbound.

	Change from Adult Values	
	Newborn	Child
Total protein	↓	=
Albumin	↓	=
α_1-Acid glycoprotein	↓	=
Fetal albumin	Present	Absent
Globulin	↓	=

Body composition, especially water and fat content, are also highly age dependent (Figure). Total body water accounts for a larger fraction of body weight than in older children and adults. There is also a predominance of extracellular water. As a result, the volume of distribution for water-soluble drugs is greater in newborns and infants when normalized to body weight or

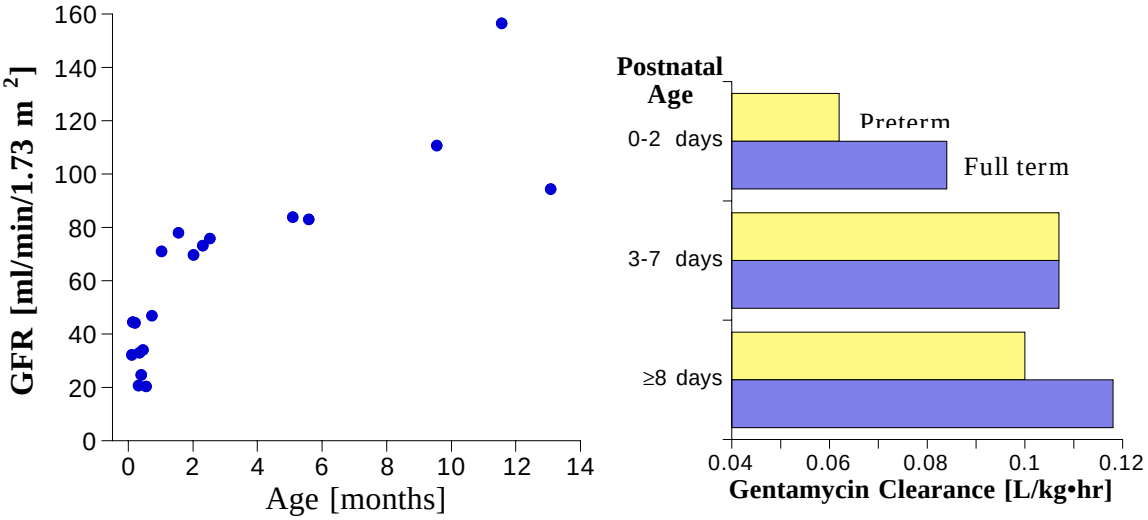


surface area. Lipid soluble drugs have a larger volume of distribution in infants, because of the higher proportion of body fat.

Drug metabolism. The capacity of the liver to metabolize drugs is lower at birth, and the rate of development of the various metabolic pathways is highly variable and may be influenced by exposure to drugs *in utero* and postnatally. Because of the variation in the maturation of drug metabolizing enzymes systems, the primary metabolic pathway for some drugs may differ in newborns and infants compared with adults. For example, glucuronide conjugation pathways are low at birth, but sulfate conjugation appears to be normal; therefore, drugs that are eliminated by conjugation with glucuronide in adults (e.g., acetaminophen) may be cleared primarily as sulfate conjugates in newborns and infants.

Generalizations about the rate of maturation of drug metabolizing enzymes systems during infancy and childhood is difficult because of the lack of data, the degree of variability and the inducibility of some systems. Oxidative capacity is reduced at birth, but appears to develop over days as evidenced by the decline in the half-life of phenytoin ($t_{1/2}$ >200 hrs in the first 5 days of life compared with 50 hrs by 30 days of life). During childhood, oxidative capacity for drugs exceeds that in adults, especially when expressed per body weight. In contrast, alcohol dehydrogenase does not approach adult levels until 5 years of age. The development of other phase I reactions (e.g., hydrolysis, demethylation) have not been well characterized. Glucuronidation is reduced at birth and does not approach adult levels until 3 years of age, whereas sulfate conjugation is active *in utero* and at birth and declines in importance with age.

Renal excretion. At birth renal function is limited, because the kidneys are anatomically and functionally immature. Renal blood flow is 40 ml/min/kg in newborns (16% of cardiac output), and reaches adult values by 1 year of age (20-25% of cardiac output). In full term newborns, glomerular filtration rate is 10-15 $ml/min/m^2$ and in premature infants the GFR is only 5-10 $ml/min/m^2$. GFR doubles by 1 week of age, because of a postnatal decrease in renal vascular resistance. GFR reaches adult values by 1 year of age (Figure, left). A glomerular/tubular imbalance is present at birth, because of the greater maturity of glomerular function in newborns. Renal tubular secretory function is impaired at birth, and approaches adult values by 1 year of age. Renal clearance of drugs is delayed in newborns and young infants, necessitating dose reductions (Figure, right), but after 8-12 months of age, the renal excretion of drugs is comparable with



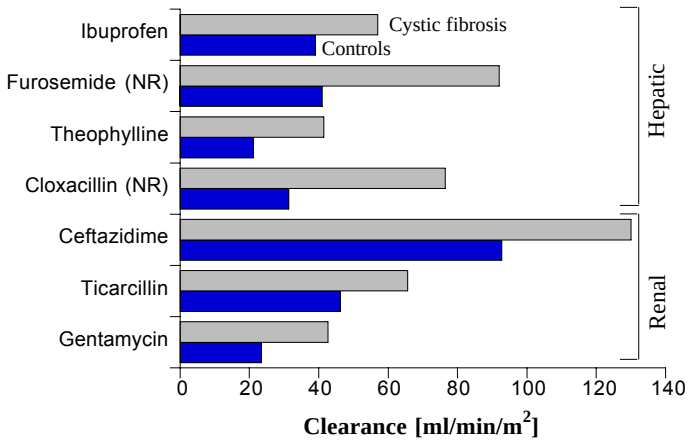
that observed in older children and may even exceed that in adults. In young children, renal size relative to body surface area is larger than in adults and drug clearance normalized to body surface area can exceed that in adults. The dose of aminoglycosides in children required to achieve equivalent plasma drug concentrations is usually 1.5- to 2-fold higher than in adults, because of the more efficient renal clearance in children. The dosing interval in children may need to be shorter (q6h instead of q8h).

THERAPEUTIC IMPLICATIONS OF GROWTH & DEVELOPMENT

Drug effect is related to the drug concentration at the target site, and the concentration at the target site is determined by the dose and disposition (pharmacokinetics) of the drug. The developmental changes in body composition and excretory organs have a significant impact plasma drug concentration and concentration at the target site, and these changes must be taken into account when calculating doses for infants and children of different ages. The rapid changes that occur postnatally may require frequent dose adjustments during the first few weeks of life. Antibiotic doses, for example, are frequently increased after the first 7 days of life, to account for the initial rapid increase in renal function.

The rapid growth in body mass and change in excretory organ function means that a single dose recommendation for all age groups within the pediatric population is not sufficient to account for these changes. For example, theophylline dose changes during childhood to compensate for changes in clearance. In infancy (<12 months), the infusion rate is 0.3-0.6 mg/kg/hr, during childhood, it is 0.8 mg/kg/hr for children 1-9 years old and 0.7 mg/kg/hr for children 9-12 years old. Adolescents are treated with 0.5 mg/kg/hr. The higher doses during early childhood reflect the enhanced metabolic capacity in this age group when normalized to body weight. The liver size as a % of total body weight also peaks during early childhood.

The effect of normal growth and development on the pharmacodynamics of drugs has been less well studied. Age-dependent variation in receptor number, receptor affinity for drugs, or the responsiveness of the target organ or tissue to receptor occupancy could influence drug effect. Drugs may also alter the growth and development process or express effects that are dependent on the stage of development, such as the enamel dysplasia caused by tetracycline in young children or the depression of linear growth by corticosteroids.



The spectrum of diseases that occur in the pediatric population are also quite different than diseases that afflict adults, and the effect of pediatric diseases on the pharmacokinetics and pharmacodynamics of the drugs used to treat these diseases requires more study. In cystic fibrosis, which is an inherited disorder of chloride transport that causes inspissated secretions leading

to tissue damage in a variety of organs (including the liver) and tissues, the clearance of a wide variety of drugs is actually enhanced (Figure, above). Larger doses per kg of bodyweight are required in these patients to achieve equivalent plasma drug concentrations compared with normal children.

Consideration of the impact of developmental changes occurring throughout infancy, childhood, and adolescence will lead to more rational and safer and more effective use of drugs in these populations.

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